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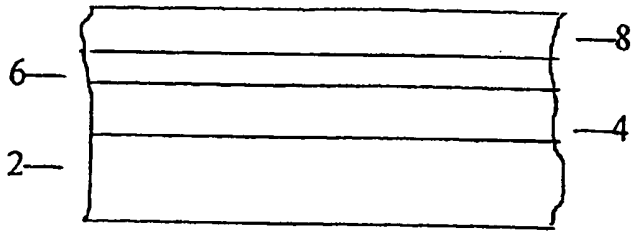
(54) Title: ENZYMATIC TREATMENT AND PREVENTION OF HYPERTROPHIC SKIN

(57) Abstract

The invention relates to use of at least one enzyme selected from collagenase and hyaluronidase, in admixture with at least one water soluble carrier composition which comprises at least one biocompatible cold water soluble polymer, in the manufacture of a dressing for topical application, which includes said composition in the form of layer film, for slow release. The dressing possesses sufficient flexibility and coherence, so that it can be produced in rolls or sheets. The invention enables simultaneous treatment of a broad skin area, which after treatment may be washed to remove residual water-soluble polymer. The composition may be utilized in the form of patches comprising an absorbent layer (4) supporting a thin layer (6) of inventive composition, and adhered to a non-absorbent backing layer (2), while covered by a thin peelable layer (8).



Active in transdermal system.

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ENZYMATIC TREATMENT AND PREVENTION OF HYPERTROPHIC SKIN

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a topical therapeutic composition, a dressing including it and use of enzymes in its manufacture.

Wounds may be defined as damage to the skin, and may be caused by a scratch, heat, cold, chemical or radioactive substances, electricity, etc. The term "wound" includes burns and scars. The skin is one of the most important sensory organs in the body arid it is the body's defensive mechanism against the environment. When part of the skin is damaged, water, salts, proteins and energy are liable to be leaked out of the body through the damaged skin. Fungi and bacteria may cause local infection in the wound, with the threat of deeper penetration into the body, resulting in substantial inflammation.

The purpose of treating wounds is to repair the damage caused to the skin. If the damage is restricted and local, cure will usually take a few days, or perhaps weeks. However, if the damaged area is extensive and severe, the curing process will be slow and skin implantation and other treatments, e.g. drug administration, may well be essential. Often, curing wounds involves severe pain, leaves scars and requires physiotherapy and/or psychological treatment; in severe cases the treatment will have to deal with such problems as bleeding, contamination, pains, poisons, water accumulation, etc.

Many methods are currently in use for treating wounds, e.g., antiseptic and antibiotic preparations, laser illumination, cryotechniques, native enzyme preparations, etc., see for example Krantz and Cart, Pharmacological Principles of Medical Practice, Eighth Edition, 1972, pp. 1001-1003, "Agents for Treatment of Burns and Ulcers"; Goodman and Gilman, Pharmacological Basis of Therapeutics, Sixth Edition, 1980, pp. 964-987. Each method of treatment has both its advantages and disadvantages.

Among these methods, the use of native enzyrnes to treat wounds is quite common. These enzymatic preparations are generally based on e.g. proteolytic enzymes such as trypsin and chymotrypsin (which cleanse

purulent-necrotic wounds and reduce the amount of pathogens), lysozyme (which dissolves bacteria cell walls), and/or collagenase (which decomposes collagen and prevents formation of rough scars). Enzymatic preparations usually take the form of gels, powders or liquids, which are spread on the wounds. The use of native proteolytic enzymes to treat wounds is quite common. However, this method suffers from some major shortcomings, e.g. native enzymes are rapidly inactivated by inhibitors, they are unstable in aqueous solutions, exhibit antigen and pyrogen properties, may penetrate into blood circulation and give rise to an allergic reaction, besides being relatively expensive.

In attempts to overcome these disadvantages, some researchers have covalently coupled various proteolytic enzymes onto polymeric beads, of approximately 0.05-0.5 mm average diameter, composed of dextran dialdehyde and/or dialdehyde cellulose, see J. Turkova et al., Can. Pat. 1217134 (1987); C. Flemming et al., Acta Biol. Med. Ger. 31: 449 (1973). However, use of these conjugated beads for treating wounds is limited because of a number of disadvantages, e.g., this method is relatively expensive, and liquid frequently flows from the wounds and sweeps away the beads, making it necessary to repeat the treatment several times. Further major shortcomings of these dialdeyde polymers for treatment of wounds have been mentioned above.

A method for treating wounds, developed in recent years (see SU N117365, 1981 and SU N210938, 1984), is based on covalent binding of bioactive reagents, e.g. proteolytic enzymes, onto dialdehyde cellulose dressings and/or aldehyde polycaproamide dressings. Exemplary of such dressings are those formed by acid hydrolysis of polycaproamide, followed by reaction of glutaraldehyde with terminal amino groups in the hydrolysate. Immobilized enzyme dressings of this type solved the problem of the previous polyaldehyde beads (i.e. they tend to be removed from the wounds by liquid flowing therefrom), but apparently still did not solve other problems such as leakage of bound enzymes into the body liquid and poor mechanical properties.

The protein collagen is important in the wound healing process. However, wounds, whether accidental or intentional (e.g. resulting from

surgery), often give rise in the healing stages to what appears to be a random accumulation of tissue rich in collagen and proteoglycan. Keloids are tumors which occur in the dermis, usually following trauma, and they often recur after surgical removal. Hypertrophic scars are tissue accumulations, frequently disfiguring, the removal of which is problematic. Depressed scars result from contraction of the skin (e.g., in normal healing following inflammatory acne); they are usually both permanent and unsightly. Acne vulgaris often causes undesirable scarring. Post-surgical adhesions, which are a common complication of surgery, and also wrinkling, cellulite formation and neoplastic fibrosis, appear to involve excessive collagen formation.

For convenience, undesired hypertrophic accumulations of collagen such as are described in the preceding paragraph, will be referred to collectively herein as "hypertrophic skin accumulations". Their dissolution or prevention by administration of collagenase and optionally also hyaluronidase, directly into the lesion or the affected area, in practice by injection, is described for example in U.S. 4,524,065; see also, Friedman, K., et al., Brit. J. Dermatol., 1986, 115: 403-8.

U.S. 5,516,673 describes a process for conjugating, i.e. covalently bonding, an amino compound such as an enzyme, to a polyhydroxy-polymer such as cellulose, other polysaccharide, or polyvinyl alcohol The enzyme may be e.g. trypsin, chymotrypsin, lysozyme, collagenase or hyaluronidase, and the polymer may be in the form of a bandage or patch, which finds utility in the treatment of wounds, including scars and bums.

In WO 9615236, similar to U.S. 5,516,673, the polymer or its functional derivative, is conjugated with cross-linked biologically active protein, e.g. an enzyme. As before, the product may take the form of a powder, bandage or patch, for application to wounds, including bums and scars.

US 4,399,123 describes a product made by treating mammalian fibrous tissue with proteolytic enzyme (I) and then with a carbohydrate-splitting enzyme (II) (e.g. amylase, hyaluronidase or neuramidinase). The product is used as skin tissue transplantation for permanent repair or as a temporary dressing for cutaneous wounds and soft tissue injuries.

DE 3139089 describes us of proteinaceous (e.g. collagen) sheets as carriers for th rapeutically active non-immobilized enzymes for application to the skin including wound dressings. The sheets may contain hyaluronidase in combination with therapeutically active substances.

In US 5,552,162, scars are treated by covering with a thermal insulating material, possibly containing a medicament such as a calcium antagonist, in order to elevate the surface temperature of the scar, and thus stimulate collagenase activity therein.

Exemplary of numerous skin- or burn-treating compositions is that of US 4,154,823, which comprises p-aminobenzoic acid, Ca d-pantothenate and α-tocopherol, and optionally aloe, Kava Kava and/or methyl salicylate.

The entire disclosures of the literature and patent references mentioned herein are explicitly incorporated by reference in the present patent application.

OBJECTS OF THE INVENTION

It is a general object of the present invention to provide a therapeutic composition, for external use in the prevention and treatment of hypertrophic skin accumulations.

Another general object of the invention is to provide such a composition characterized by the absence of covalent bonding between the carrier and the therapeutically active substance(s).

A still further general object of the invention is to provide such a composition for topical administration, characterized by the fact that release of active substance to the desired locus of treatment is initiated and regulated by the action of moisture in the skin.

Yet a further general object of the present invention relates to use of enzymes (and optionally other therapeutically active and/or other skin treating ingredients) in the manufacture of a slow-release therapeutic composition for prevention and treatment of hypertrophic skin accumulations.

It is moreover an object of the present invention to provide a slow-release therapeutic composition for topical administration in the prevention and treatment of hypertrophic skin accumulations.

A further object of the present invention is to provide an enzymatic composition having the mentioned characteristics.

Another object of the invention is to provid such a composition in the form of a thin layer or film.

Still an additional object of the invention is to provide a composition of the type mentioned which may be used also for skin treatment following a cosmetic skin operation.

Other objects and advantages of the invention will appear from the description, which follows.

SUMMARY OF THE INVENTION

In one aspect, the present invention accordingly provides a dressing for topical application in the prevention and treatment of hypertrophic skin accumulations and which possesses sufficient flexibility and coherence, such that it can be produced in rolls or sheets, from which portions may be cut to a desired size, which dressing consists of or comprises, a layer or film of a water soluble composition comprising, and designed for slow release of, at least one active ingredient selected from collagenase and hyaluronidase, in admixture with at least one carrier which comprises at least one biocompatible cold water soluble polymer. The term "slow-release" in the present specification and claims means slow release of therapeutically active substance(s) from the said water soluble composition.

In another aspect, the present invention provides use of at least one enzyme selected from collagenase and hyaluronidase, in admixture with at least one water soluble carrier composition which comprises at least one biocompatible cold water soluble polymer, in the manufacture of a dressing for topical application which includes said composition in the form of a layer or film, for slow release of said enzyme in treatment of hypertrophic skin accumulations and in the healing process of wounds and burns, excluding open wounds, provided that said dressing possesses sufficient flexibility and coherence, so that it can be produced in rolls or sheets, from which portions may be cut to a desired size.

In general, the term "polymer" in the present specification and claims includes both homopolymers and copolymers.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in the attached drawings in which:
Figure 1 is a sectional depiction of an embodiment of the invention; and
Figure 2 is a depiction in plan of a different embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The therapeutic composition useful in the invention is preferably further characterized by at least one of the following features: (a) the carrier is a tacky carrier; (b) the composition comprises additionally a pharmaceutically acceptable antioxidant, e.g. at least one vitamin selected from vitamins C and E; (c) the polymer contains repeating units containing at least one function selected from alcoholic, ether and ketonic functions, e.g. a polymer selected from polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, carboxymethylcellulose, agar, alginic acid and salts thereof; (d) the composition incorporates at least one further therapeutically active and/or other skin treating ingredient; (e) the composition contains a biocompatible water-soluble plasticizer, e.g., glycerol or low MW polyethylene glycol. It is believed that vitamin C and/or E may act beneficially with regard to skin metabolism, in addition to their antioxidant activity. The further therapeutically active and/or skin treating ingredient(s) may be exemplified by a steroidal antiinflammatory agent, such as prednisolone or triamcinolone acetonide and/or a non-steroidal such agent, e.g. a scopolamine derivative, for example anisodine, or e.g. any of the ingredients (therapeutically active or otherwise, taken alone or in any combination) specified in US 4,154,823.

In contrast to what is described in SU N117365 and SU N210938, and in U.S. 5,516,673 and WO 9615236, the present compositions are characterized *inter alia* by the absence of covalent bonding between the carrier and the therapeutically active substance(s). The immobilization of the enzymes in these patents is believed to be contrary to what is desirable in the treatment of

hypertrophic skin accumulations, as being liable to reduce the activity of active sites in the enzyme and to prevent mobility, whereas mobility is considered advantageous, in the present context.

While the present invention is not regarded as limited in scope by any theory, it is presently believed that the enzyme molecules are bound loosely to the carrier, possibly by Van der Waals or/and coordinate or hydrogen bonding, and that these bonds are slowly destroyed by the moisture released by the skin, when the composition, which is water-soluble, is applied thereto.

As stated above, the invention in one aspect relates to a dressing for topical application in the prevention and treatment of hypertrophic skin accumulations. In a particular embodiment, the dressing may be configured as a patch of laminar construction comprising an absorbent layer supporting at least one thin layer of the composition, adhered to a non-absorbent backing layer, and being covered by a thin peelable protective layer, wherein the absorbent layer may optionally contain the composition. A plurality of therapeutically active and/or other skin-treating ingredients and/or vitamin C and/or E, when present, may be located in the same layer or film, and/or in different adjacent layers or films.

The invention will be illustrated by the following Examples of the composition of the invention.

Example 1

High purity lyophilized collagenase (typically Sigma C0773) is thoroughly mixed with cold water soluble polyvinyl alcohol (Sigma P8136), such that the mixture contained per ml, 500, 750 or 1000 units collagenase.

Example 2

Salt-free lyophilized hyaluronidase (typically Sigma H3884) is thoroughly mixed with cold water soluble polyvinyl alcohol (Sigma P8136), such that the mixture contained per ml, 500, 750 or 1000 units hyaluronidase.

Example 3

The products of Examples 1 and 2 are mixed in such ratios that the resultant mixture contained per ml, either 250 or 500 units collagenase, together with 375 units hyaluronidase.

Since release of the active ingredient(s) from the admixture with carrier is to be initiated and maintained by skin moisture at the locus of application, it is desirable to store the compositions of the invention, as well as any dressings containing them, before use, in a moisture-free atmosphere.

Administration of the compositions of the invention

The present invention is not directed to the treatment of open wounds. Rather, it is concerned with preventing scar and keloid formation in circumstances where they are expected to be formed, i.e. during the healing process of e.g. wounds and burns, as well as with treating hypertrophic skin accumulations already formed. In particular, the present invention enables amelioration of hypertrophic accumulations in connective tissue, or prevention of their formation.

The composition of the invention may be, in a particular embodiment, configured as a single layer or multilayer dressing. In another embodiment, he composition may be (as a single layer or multilayer) supported on a dressing, which is then applied to the desired locus on the skin. Alternatively, the compositions may be utilized in the form of patches, e.g. as illustrated in section in Fig. 1, which shows a laminar construction (in which the individual layers 2, 4, 6 and 8 are not necessarily drawn to scale), comprising an absorbent layer 4 supporting a thin layer 6 of the inventive composition, and adhered to a non-absorbent backing layer 2, while covered by a thin peelable layer 8, which is removed immediately before use. It will be evident that many variations of this arrangement are possible, e.g. absorbent layer 4 may contain and act as a reservoir for the composition, or alternatively layer 4 may be dispensed with altogether, the composition then being supported on backing layer 2, but still being protected, if desired for many practical purposes, by peelable layer 8. In another alternative, layer 4 may instead represent a further polymeric layer containing e.g. vitamin C or E, and/or a further therapeutically active and/or other skin treating ingredient such as at least one steroidal or non-steroidal antiinflammatory agent.

in the healing of face burns, and in which the individual items shown are not necessarily drawn to scale. Mask 12 has holes or slits as necessary, for the eyes 14, nostrils 16 and mouth 18. The composition of the invention will in a particular embodiment be supported on that side of mask 12 to be applied to the face of a patient, while in a different embodiment the mask will be constituted by a self-supporting single or multi-layer or film of the inventive composition. It will be evident that many variations in the shape and size of such a mask, and of the holes or slits shown therein, are possible. In section, the mask may have a laminar arrangement in the manner illustrated in Fig. 1. Alternatively, the mask may be constructed as described in the following paragraph.

In a particular embodiment, the composition may be in the form of a thin layer or film, not necessarily requiring a backing layer. In this embodiment, such a thin layer or film will possess sufficient flexibility and coherence, so that it may be produced in rolls or sheets, from which portions may be cut to a desired size. It is contemplated that such a layer may be transparent, so that the progress of therapeutic action may be observed, and also that it may be molded against the skin surface. Moreover, when utilizing a tacky carrier, the composition will self-adhere to the locus under treatment. At the termination of treatment, the area of skin application may be washed to remove residual water-soluble polymer.

While the compositions may be applied for similar purposes as described e.g. in U.S. 4,524,065, it is believed to be self-evident that the present invention possesses marked advantages over the method of this U.S. Patent, in that, for example, it provides the possibility of treating a broad area of the skin at one time, contrasted with injection which depends on questionable diffusion from the injected site. Moreover, the requirement for repeated injections in U.S. 4,524,065 would place a strain on patient compliance, which is much less likely to arise in the present method.

While particular embodiments of the invention have been particularly described above, it will be apparent to skilled persons that the present invention is not limited thereto, since many modifications or variations can be made within the scope of the claims which follow.

CLAIMS

1. A dressing for topical application in the prevention and treatment of hypertrophic skin accumulations and which possesses sufficient flexibility and coherence, such that it can be produced in rolls or sheets, from which portions may be cut to a desired size, which dressing consists of or comprises, a layer or film of a water soluble composition comprising, and designed for slow release of, at least one active ingredient selected from collagenase and hyaluronidase, in admixture with at least one carrier which comprises at least one biocompatible cold water soluble polymer.

2. A dressing according to claim 1, wherein said composition is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier;

(b) said composition comprises additionally a pharmaceutically acceptable antioxidant.

(c) said polymer contains repeating units containing at least one function selected from alcoholic, ether and ketonic functions;

(d) said composition incorporates at least one further therapeutically active and/or other skin treating ingredient;

(e) said composition contains a biocompatible water-soluble plasticizer.

3. A dressing according to claim 1, wherein said composition is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier;

(b) said composition comprises additionally at least one vitamin selected from vitamins C and E;

(c) said polymer is selected from polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, carboxymethylcellulose, agar, alginic acid and salts thereof;

(d) said at least one further therapeutically active ingredient is selected from steroidal and non-steroidal antiinflammatory agents.

(e) said biocompatible water-soluble plasticizer is selected from glycerol and low MW polyethylene glycol.

4. A dressing according to claim 1, which is configured as a patch of laminar construction comprising an absorbent layer supporting a thin layer of said composition, the absorbent layer being adhered to a non-absorbent backing layer, and being covered by a thin peelable protective layer, wherein the absorbent layer may optionally contain said composition.

5. A dressing according to claim 4, which is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier;

(b) said composition comprises additionally a pharmaceutically acceptable antioxidant.

(c) said polymer contains repeating units containing at least one function selected from alcoholic, ether and ketonic functions;

(d) said composition incorporates at least one further therapeutically active and/or other skin treating ingredient;

(e) said composition contains a biocompatible water-soluble plasticizer.

6. A dressing according to claim 4, which is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier;

(b) said composition comprises additionally at least one vitamin selected from vitamins C and E;

(c) said polymer is selected from polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, carboxymethylcellulose, agar, alginic acid and salts thereof;

(d) said at least one further therapeutically active ingredient is selected from steroidal and non-steroidal antiinflammatory agents.

(e) said biocompatible water-soluble plasticizer is selected from glycerol and low MW polyethylene glycol.

7. A dressing according to any one of the preceding claims, which is configured as a face mask.

8. Use of at least one enzyme selected from collagenase and hyaluronidase, in admixture with at least one water soluble carrier composition which comprises at least one biocompatible cold water soluble polymer, in the manufacture of a dressing for topical application which includes said composition in the form of a layer or film, for slow release of said enzyme in treatment of hypertrophic skin accumulations and in the healing process of wounds and burns, excluding open wounds, provided that said dressing possesses sufficient flexibility and coherence, so that it can be produced in rolls or sheets, from which portions may be cut to a desired size.

9. Use according to claim 8, which is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier;

(b) said composition comprises additionally a pharmaceutically acceptable antioxidant.

(c) said polymer contains repeating units containing at least one function selected from alcoholic, ether and ketonic functions;

(d) said composition incorporates at least one further therapeutically active and/or other skin treating ingredient;

(e) said composition contains a biocompatible water-soluble plasticizer.

10. Use according to claim 9, which is further characterized by at least one of the following features:

(a) said carrier is a tacky carrier; (b) said composition comprises additionally at least one vitamin selected from vitamins C and E; (c)said polymer is selected from polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, carboxymethylcellulose, agar, alginic acid and salts thereof; (d) the composition contains a biocompatible water-soluble plasticizer; (e) said at least one further therapeutically active ingredient is selected from steroidal and non-steroidal antiinflammatory agents.(f) said biocompatible water-soluble plasticizer is selected from glycerol and low MW polyethylene glycol.

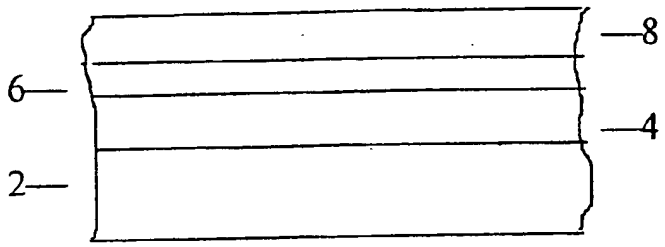

FIGURE 1

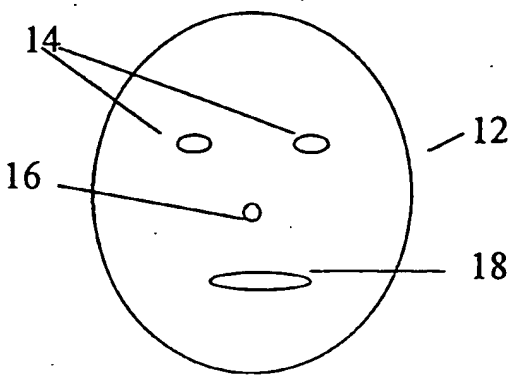

FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL99/00629

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61F 13/00; A61K 9/70
US CL :424/443, 449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/443, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: dressing, scar, polymer, collagenase, hyalorindase, carrier, anti-oxident, vitamin E

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,516,673 A (MARGEL ET AL.) 14 May 1996, abstract; col.3, lines 18-21, col.4, lines 1-9, lines 61-62, lines 67-68; col.5, lines 1-12.	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL99/00629

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,552,162 A (LEE) 03 September 1996, abstract; col. 6, lines 11-16, lines 37-38, col. 9, lines 10-17; col. 11, lines 43-46; col. 12, lines 15-16.	1-10
Y	US 4,154,823 A (SCHUTT) 15 May 1979, col. 1, lines 45-46; col. 2, lines 56-57, col. 3, lines 41-42, lines 45-50; col. 4, lines 6-9.	1-10
Y	US 5,791352 A (REICH ET AL) 11 August 1998, abstract; col. 2, lines 25-28, line 35, lines 50-66; col. 3, lines 10-15; col. 5, lines 10-16, lines 24-32, lines 41-44; col. 6, lines 17-18, lines 25-29, lines 50-52.	1-10
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